Perioperative (Neoadjuvant and Adjuvant) Apalutamide + ADT vs Placebo + ADT With Radical Prostatectomy in High-Risk Localized or Locally Advanced Prostate Cancer: Final Analysis of the PROTEUS Phase 3 Study

Mary-Ellen Taplin[1], Martin Gleave[2], Neal D Shore[3], Angela Lopez[4], Alexander Kretschmer[5], Eleni Efstathiou[6], Ronaldo Damião[7], Toshiyuki Kamoto[8], Ashley Ross[9], Alberto Briganti[10], Boris A Hadaschik[11], Axel Heidenreich[12], Alvaro Juárez Soto[13], Brendan Rooney[14], Shaozhou Ken Tian[5], Lisa Wetherhold[5], Branko Miladinovic[15], Sharon McCarthy[5], Christopher P Evans[16], Adam S Kibel[17]

[1]Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [2]Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada; [3]START Carolinas/Carolina Urologic Research Center, Myrtle Beach, SC, USA; [4]Johnson & Johnson, Los Angeles, CA, USA; [5]Johnson & Johnson, Spring House, PA, USA; [6]Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [7]Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil; [8]University of Miyazaki, Miyazaki City, Japan; [9]Northwestern University, Chicago, IL, USA; [10]Unit of Urology, Urological Research Institute (URI), IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; [11]University of Duisburg-Essen and German Cancer Consortium (DKTK)-University Hospital Essen, Essen, Germany; [12]University Hospital of Cologne, Cologne, Germany; [13]Hospital Universitario de Jerez de la Frontera, Cádiz, Spain; [14]Johnson & Johnson, High Wycombe, UK; [15]Johnson & Johnson, San Diego, CA, USA; [16]University of Nevada and Renown Health, Reno, NV, USA; [17]Mass General Brigham, Boston, MA, USA

Presented by M-E Taplin at the 2026 ASCO Annual Meeting; May 29 - June 2, 2026; Chicago, IL, USA

Key Takeaways In High-Risk Localized or Locally Advanced Prostate Cancer (HR-LPC) PROTEUS Is the First to Demonstrate

1

1 year of perioperative apalutamide and androgen deprivation therapy significantly improves MFS

2

Significant improvement in major pathological response at prostatectomy

3

Significant improvement in EFS and delayed time to subsequent therapy

… setting the bar for a new standard of care

EFS, event-free survival. MFS, metastasis-free survival.

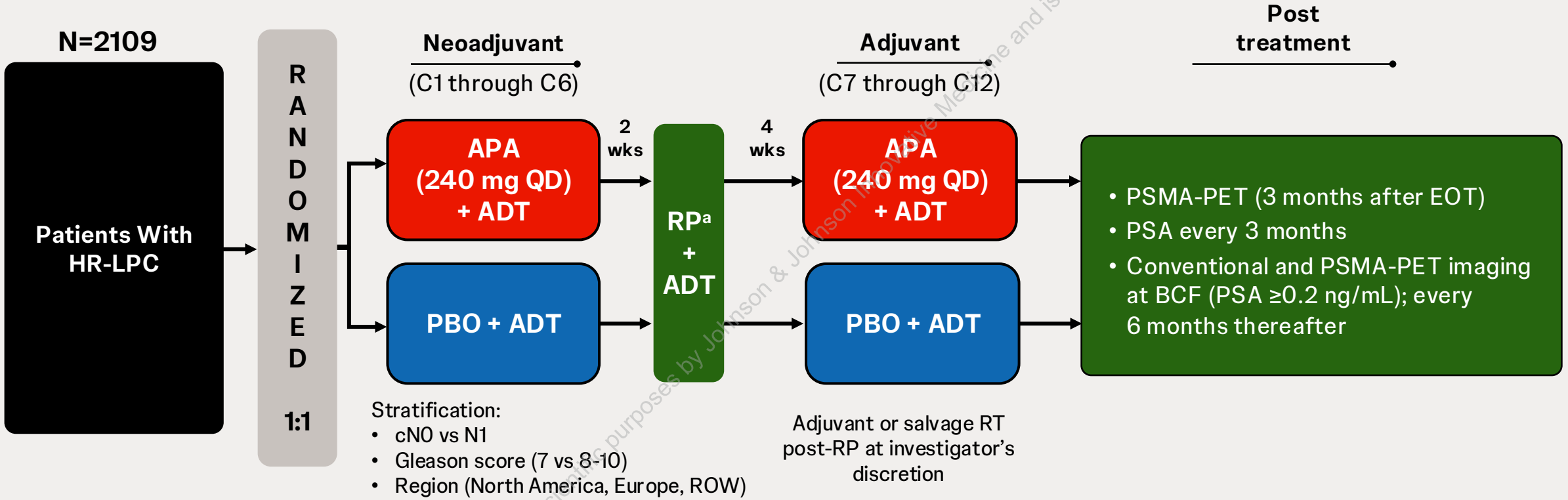
Background: Unmet Need for Treatment of HR-LPC

- Despite refinement of RP as a curative-intent therapy for patients with high-risk disease,[1] more than half will relapse, incurring morbidity from subsequent therapy[2-3]
  - Development of metastasis is associated with poor prognosis: median time from development of metastases to death has been shown to be 3-5 years[4-6]
- The ARPI apalutamide is effective in mCSPC and nmCRPC and showed favorable activity in the neoadjuvant setting in phase 2 trials[7-10]
- PROTEUS was conducted to determine whether the addition of 1 year of neoadjuvant/adjuvant apalutamide + ADT, versus placebo + ADT, improves pathological response and long-term outcomes

ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; RP, radical prostatectomy.

1. Cooley LF, Shore ND. *Transl Androl Urol.* 2025;14:493-495. 2. Eiber M, et al. *J Clin Oncol*. 2024;42:5027. 3. Stattin P, et al. *BJU Int*. 2024;134:96-102. 4. Xie W, et al. *Ann Oncol.* 2024;35:285-292. 5. Freeland S, et al. *Target Oncol*. 2025;20:139-148. 6. Stensland K, et al. *Urology*. 2024;184:135-141. 7. Chi KN, et al. *N Engl J Med.* 2019;381:13-24. 8. Smith MR, et al. *N Engl J Med.* 2018;378:1408-1418. 9. Giesen A, et al. *Eur Urol Oncol*. 2025 Dec 29:S2588-9311(25)00331-1. 10. McKay RR, et al. *J Urol.* 2021;206:80-87.

PROTEUS: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study in HR-LPC



- To complement these data, a substudy is ongoing to further inform on the role of APA + ADT + RP versus RP alone

Patients randomized from July 15, 2019, to June 30, 2022.
Protocol Amendment 7 for including PSMA-PET into MFS assessment (April 14, 2022).

APA, apalutamide; BCF, biochemical failure; C, cycle; EOT, end of treatment; PBO, placebo; PSA, prostate-specific antigen; PSMA-PET, prostate-specific membrane antigen positron emission tomography; QD, daily; ROW, rest of the world; RT, radiation therapy.
[a]APA/PBO is stopped 2 weeks prior to planned RP and then resumed 4 weeks after RP. Cardiovascular risk prophylaxis and venous thromboembolism prophylaxis given based on risk.

End Points and Hierarchical Testing:

Dual primary, assessed by BICR

- pCR/MRD (ypT0 or ≤ypT2; ≤5 mm tumor)
- MFS (metastasis by conventional or PSMA-PET[a] imaging or histopathology, or death)

Secondary (in hierarchical testing order)

- EFS
- Time to first subsequent therapy
- TTDM by conventional or PSMA-PET imaging
- NED at 4 years
- MFS (by conventional imaging)
- Time to PSA-free survival with testosterone recovery[b]

Additionally, exploratory end points included RCB, OS for no detriment of treatment, and testosterone recovery >200 ng/dL

BICR, blinded independent central review; MRD, minimal residual disease; NED, no evidence of disease; pCR, pathological complete response; OS, overall survival; RCB, residual cancer burden; TTDM, time to distant metastasis.
[a]Imaging was assessed by BICR. [b]Not formally tested after MFS by conventional imaging was insignificant.

PROTEUS Statistical Analysis Plan

Based on 2000 Accrued Patients

Dual Primary End Points	pCR/MRD	MFS
Alpha (2 sided)	0.01	0.04
Power	94%	85%
Number of events needed at final analysis	≥5% difference between arms	477 (Actual 472)

- pCR/MRD and MFS were to be tested at the two-sided alpha levels of 0.01 and 0.04, with alpha allocated to pCR/MRD allowed to be recycled to test MFS when pCR/MRD and EFS were both statistically significant
- As pCR/MRD and EFS were significant at the 0.01 level, MFS and the secondary end points were tested hierarchically at the level of 0.0416

Power for MFS analysis was based on assumption of HR=0.75
Power for pCR/MRD was based on assumption of 5% pCR/MRD rate in PBO + ADT arm.

The independent data monitoring committee recommended continuing blinding until the final analysis.

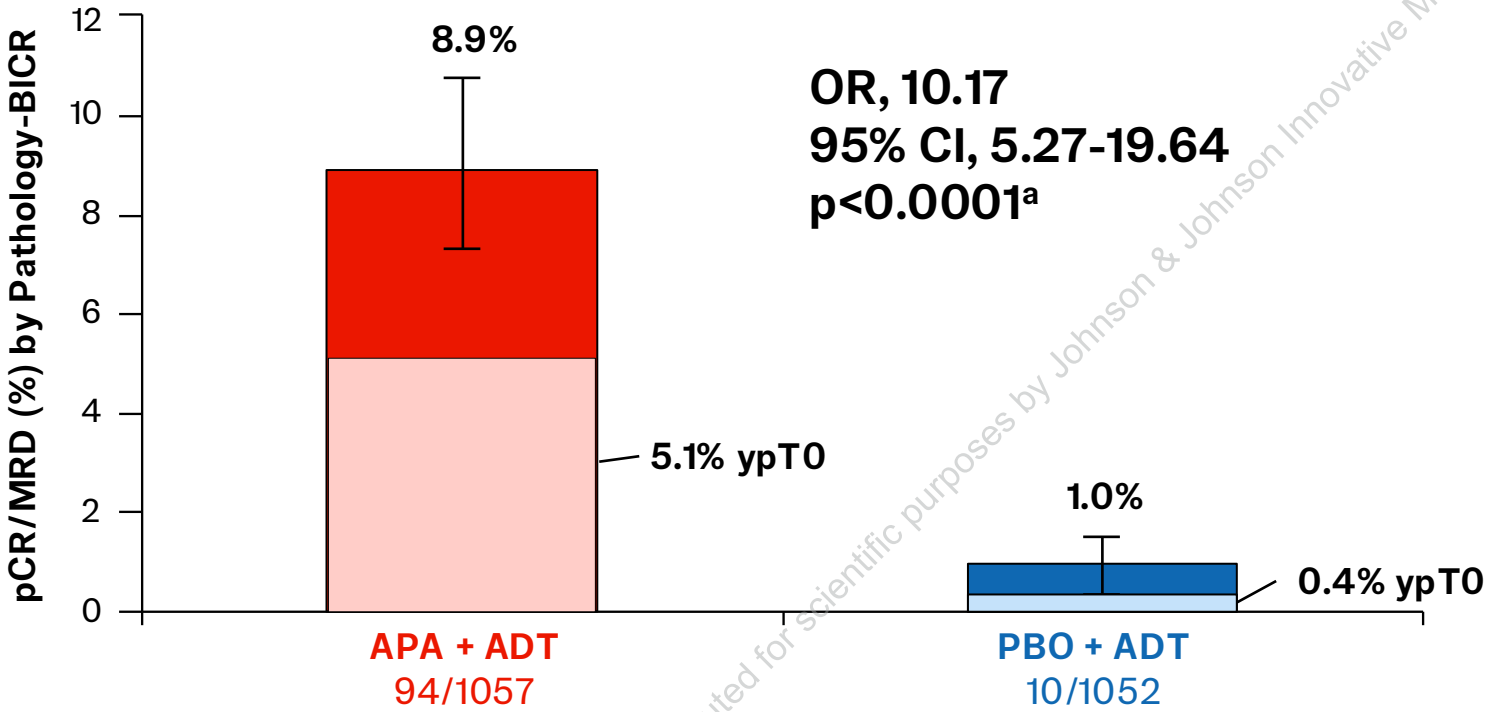
Baseline Characteristics Were Well Balanced

		APA + ADT (n=1057)	PBO + ADT (n=1052)
Median age (IQR), years		66.0 (62-71)	66.0 (61-70)
≥75, n (%)		106 (10.0)	94 (8.9)
Gleason score at initial diagnosis, n (%)	7	45 (4.3)	44 (4.2)
	≥8	1012 (95.7)	1008 (95.8)
Baseline PSA[a]	Median (IQR), ng/mL	14.4 (8.3-29.2)[b]	15.1 (8.1-33.7)[c]
	<20, n (%)	630 (61.5)	604 (58.5)
	≥20, n (%)	395 (38.5)	429 (41.5)
Tumor stage at diagnosis, n (%)[d]	≤T2	684 (64.7)	667 (63.4)
	≥T3	371 (35.1)	377 (35.8)
Regional lymph node stage at diagnosis, n (%)	N0	928 (87.8)	922 (87.6)
	N1	129 (12.2)	130 (12.4)

- **Median follow-up:** 61.7 months at clinical cutoff: (February 2, 2026); 85.1% (APA + ADT, n=899) and 87.6% (PBO + ADT, n=922) were still on the study

IQR, interquartile range.
[a]PSA before first dose was the closest value assessment on or prior to ADT or APA start date. [b]n=1025. [c]n=1033. [d]Tx: APA + ADT, 2 (0.2); PBO + ADT, 8 (0.8).

Dual Primary End Point Met: pCR/MRD



9-fold improvement in pCR/MRD at RP after 6-cycle neoadjuvant APA + ADT vs PBO + ADT

Exploratory end point of RCB (≤ypT2, N0, ≤0.25 cm^3) corroborates pCR/MRD:

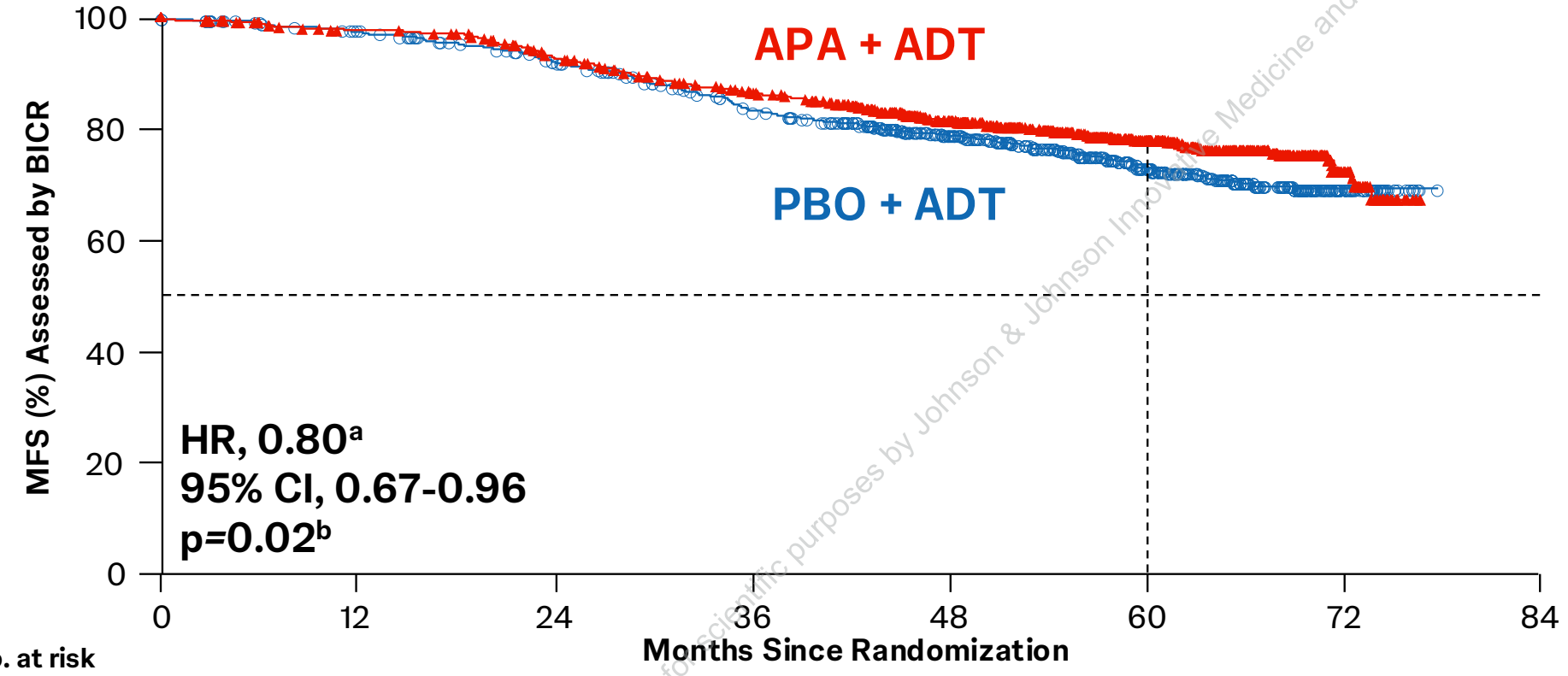
- APA + ADT vs PBO + ADT, 30.6% vs 11.7%
- OR, 3.36; 95% CI, 2.67-4.23; p<0.0001

pCR/MRD: Minimal residual tumor ≤5 mm (greatest dimension of largest tumor lesion) in prostate-confined disease (≤ypT2, N0) or no tumor identified (ypT0)
RCB: Residual cancer burden ≤0.25 cm^3 in prostate-confined disease (≤ypT2, N0)

Error bars indicate 95% confidence intervals (CIs). Odds ratio (OR) is from a logistic regression adjusted for stratification factor; OR >1 favors APA + ADT.
[a]p Value is based on Cochran-Mantel-Haenszel test stratified by Gleason score (7, ≥8), nodal status (N0, N1), geographic region (North America, Europe, and rest of the world).

Dual Primary End Point Met: MFS by Conventional or PSMA-PET Imaging

PRIMARY END POINT



No. at risk							
APA + ADT	1057	992	922	837	659	382	62	0
PBO + ADT	1052	1000	924	812	634	385	61	0

20% reduction in the risk of metastasis or death after 1 year of perioperative APA + ADT with RP by BICR

Investigator-assessed MFS was consistent:

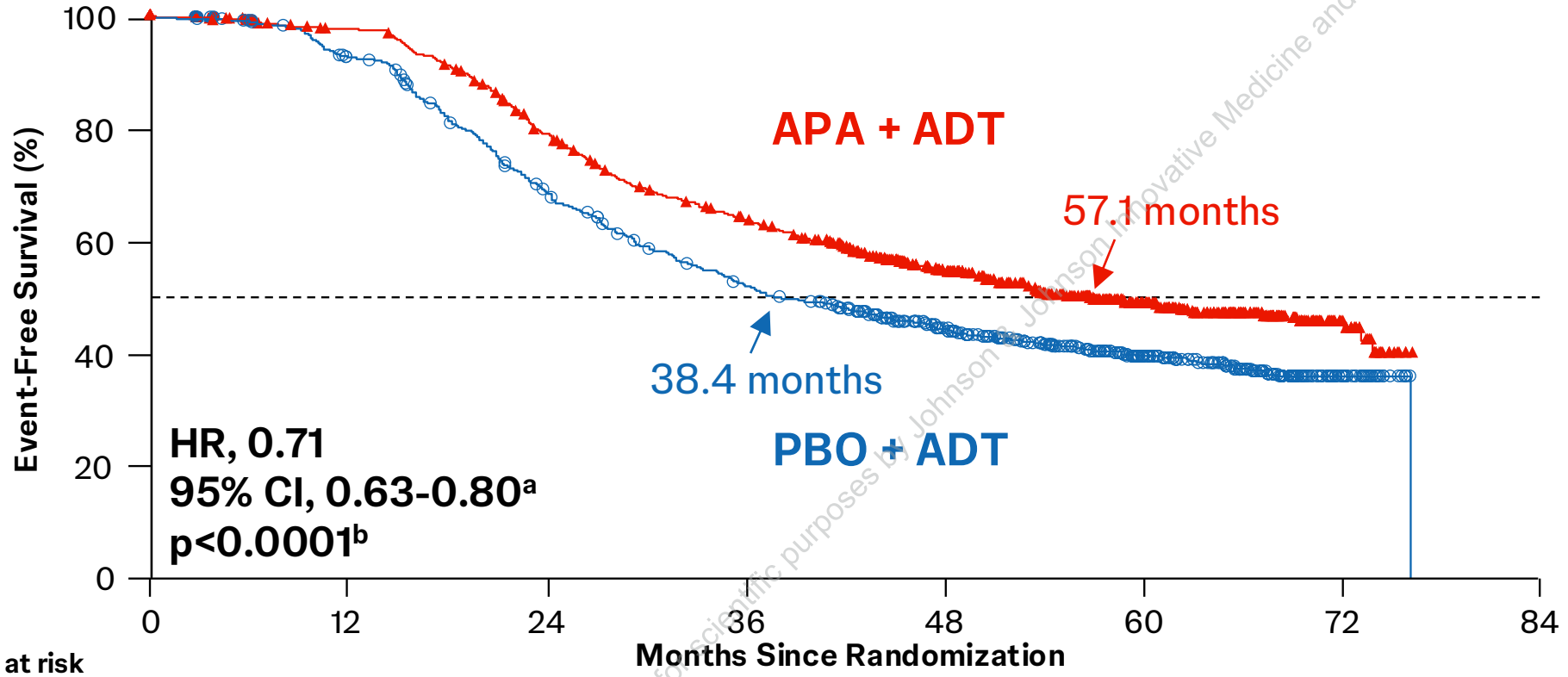
- HR, 0.74; 95% CI, 0.62-0.87; p=0.0004

MFS: Time to first occurrence of radiographic distant metastasis based on conventional imaging or PSMA-PET imaging, pathologic finding of distant metastasis, or death from any cause

[a]Hazard ratio (HR) is from stratified proportional hazards model. HR <1 favors APA + ADT.
[b]p Value is from a log-rank test stratified by Gleason score (7, ≥8), nodal status (N0, N1), geographic region (North America, Europe, and rest of the world).

KEY SECONDARY END POINT

Event-Free Survival



No. at risk							
APA + ADT	1057	988	788	625	452	246	45	0
PBO + ADT	1052	952	699	522	382	223	48	0

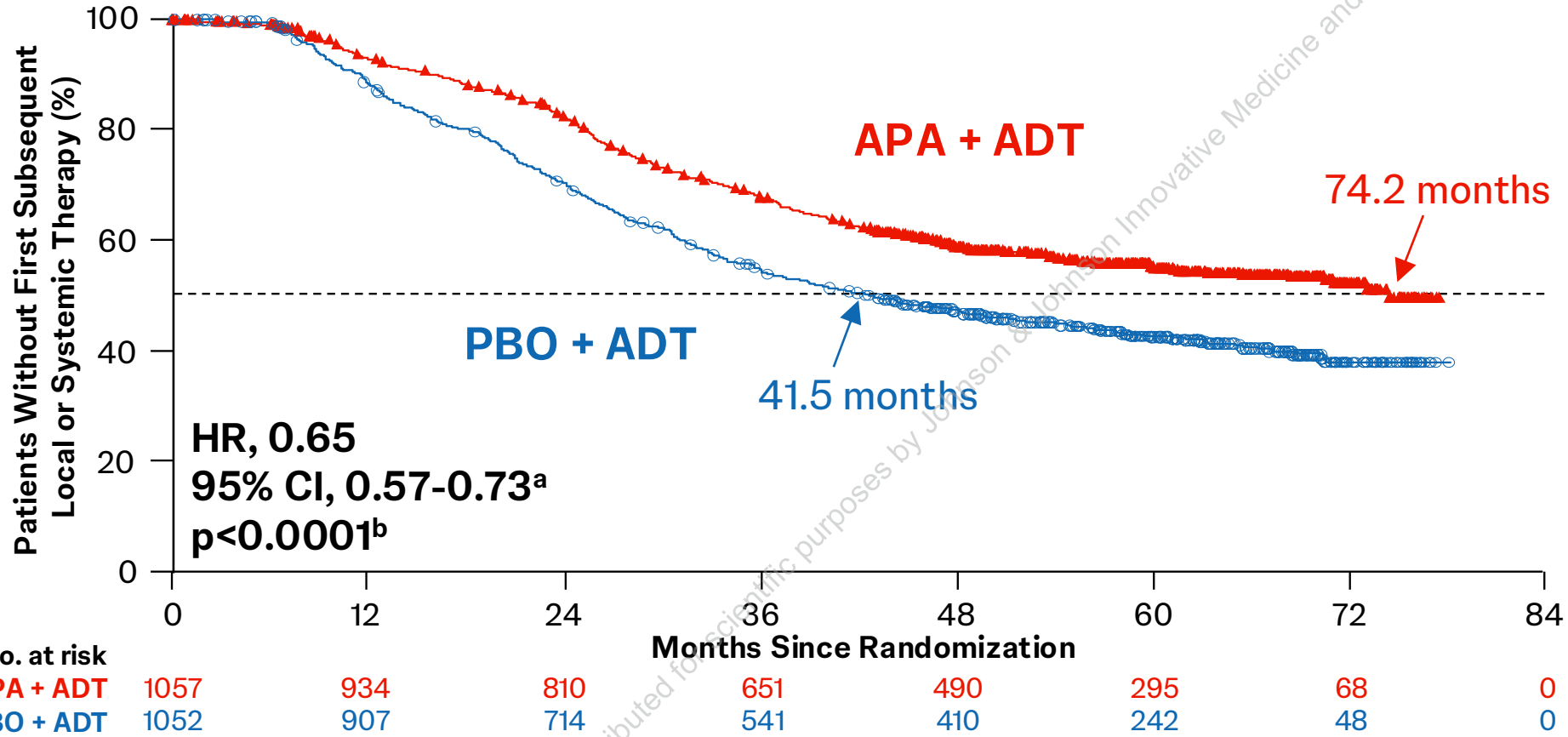
29% reduction in the risk of oncologic event or death

EFS: Time to first of BCF (PSA progression) or local or regional recurrences or distant metastasis, or death by any cause

[a]HR is from stratified proportional hazards model; HR <1 favors APA + ADT.
[b]p Value is from a log-rank test stratified by Gleason score (7, ≥8), nodal status (N0, N1), geographic region (North America, Europe, and rest of the world).

KEY SECONDARY END POINT

Time to First Subsequent Therapy



No. at risk							
APA + ADT	1057	934	810	651	490	295	68	0
PBO + ADT	1052	907	714	541	410	242	48	0

Nearly 3 years' treatment-free interval added with APA + ADT compared with PBO + ADT

Time to first subsequent therapy: Time to local, regional, or systemic therapy, including reinitiation of ADT

[a]HR is from stratified proportional hazards model; HR <1 favors APA + ADT.
[b]p Value is from a log-rank test stratified by Gleason score (7, ≥8), nodal status (N0, N1), geographic region (North America, Europe, and rest of the world).

KEY SECONDARY END POINT

Time to First Subsequent Therapy

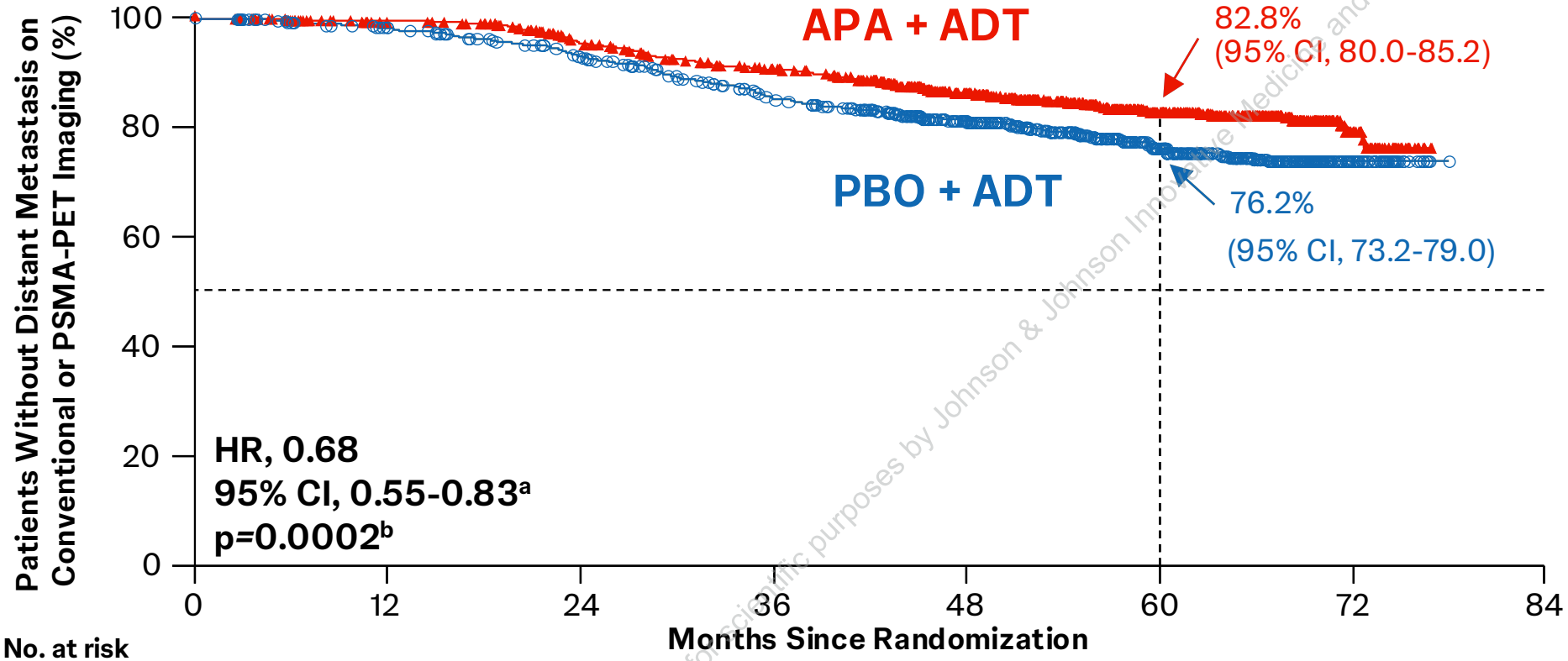
ITT Population	APA + ADT (n=1057)	PBO + ADT (n=1052)
Events, n (%)	448 (42.4)	597 (56.7)
Subsequent systemic therapy	282 (26.7)	383 (36.4)
Postoperative radiotherapy	137 (13.0)	194 (18.4)
Other radiotherapy	20 (1.9)	13 (1.2)
Subsequent surgery	9 (0.9)	7 (0.7)

Time to first subsequent therapy: Time to local, regional, or systemic therapy, including reinitiation of ADT

ITT, intent to treat.

KEY SECONDARY END POINT

Time to Distant Metastases



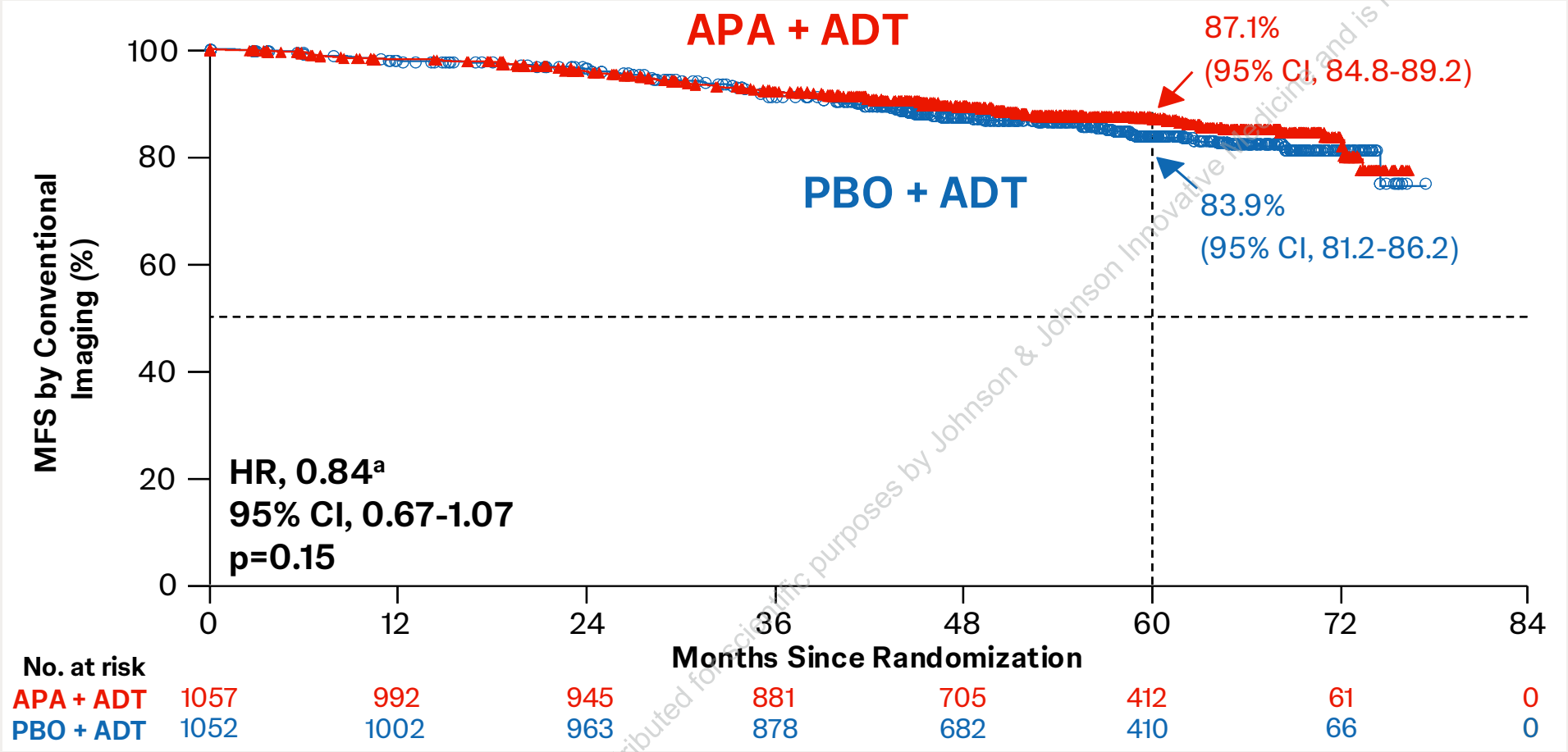
32% reduced risk of distant metastasis after APA + ADT, with 83% patients without distant metastasis at 5 years

Time to distant metastasis: Time to first distant metastasis by conventional or PSMA-PET imaging, or pathologic finding of distant metastasis

[a]HR is from stratified proportional hazards model; HR <1 favors APA + ADT.
[b]p Value is from a log-rank test stratified by Gleason score (7, ≥8), nodal status (N0, N1), geographic region (North America, Europe, rest of the world).

KEY SECONDARY END POINT

MFS by Conventional Imaging



Use of PSMA-PET with potential early detection of metastasis and subsequent therapy may impact MFS by conventional imaging

MFS: Time to first occurrence of radiographic distant metastasis based on conventional imaging, pathologic finding of distant metastasis, or death from any cause
Patients progressing on PSMA-PET and receiving subsequent treatments are included in this analysis which may delay the onset of metastasis on conventional imaging

NS, not significant.
[a]HR is from stratified proportional hazards model. HR <1 favors APA + ADT.

Testosterone Recovery

	APA + ADT (n=1050)			PBO + ADT (n=1050)		
Testosterone group	≥200	100-199	50-99	≥200	100-199	50-99
n (%)	857 (81.6)	72 (6.9)	51 (4.9)	871 (83.0)	60 (5.7)	44 (4.2)
Median age, years (range)	66 (41-83)	71 (57-84)	69 (49-83)	66 (44-81)	69 (52-80)	69.5 (51-82)

- For the patients who had testosterone recovered to ≥200 ng/dL,
  - Median testosterone value was 270 ng/dL (range, 200-1797) with APA+ADT compared with 290 ng/dL (200-1134) with PBO+ADT
  - Median time from EOT to testosterone recovery was 8.1 months with APA+ADT compared with 6.6 months with PBO+ADT

SECONDARY END POINT

Frequency of Treatment-Related Adverse Events

	Safety Population, n (%)	APA + ADT (n=1050)	PBO + ADT (n=1050)
All grades	Treatment-related AE	1000 (95.2)	985 (93.8)
Grade 3/4	Treatment-related AEs	289 (27.5)	198 (18.9)
	Treatment-related AEs leading to dose reduction[a]	118 (11.2)	24 (2.3)
	Treatment-related AEs leading to dose interruption[a]	126 (12.0)	46 (4.4)
All grades	Treatment-related AEs leading to death[b]	7 (0.7)	1 (0.1)

AE, adverse event.
Treatment-related AEs are those that occurred on or after the first dose of study drug through the last dose of study treatment + 30 days or prior to the start of subsequent therapy, whichever is earlier, or any AE that is considered treatment related regardless of the start date of the event. An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study drug (apalutamide or placebo), ADT, or RP.
[a]AEs leading to treatment interruption or dose reduction are based on AE action taken. [b]Includes grade 5 events; AEs leading to death are based on AE outcome of fatal.

Treatment-Emergent Adverse Events of Special Interest

Special Interest Category, n (%)	APA + ADT (n=1050)		PBO + ADT (n=1050)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
≥1 TEAE of special interest	398 (37.9)	90 (8.6)	214 (20.4)	23 (2.2)
Skin rash	346 (33.0)	62 (5.9)	161 (15.3)	3 (0.3)
Fall	34 (3.2)	6 (0.6)	29 (2.8)	5 (0.5)
Ischemic heart disease	25 (2.4)	13 (1.2)	22 (2.1)	9 (0.9)
Nonpathological fracture	22 (2.1)	6 (0.6)	19 (1.8)	5 (0.5)
Cerebrovascular disorders	8 (0.8)	5 (0.5)	13 (1.2)	6 (0.6)
Seizure	2 (0.2)	2 (0.2)	1 (0.1)	0
Fatigue	291 (27.7)	4 (0.4)	281 (26.8)	1 (0.1)

TEAE, treatment-emergent AE.
TEAEs are those that occurred on or after the first dose of study drug through the last dose of study treatment plus 30 days or prior to the start of subsequent therapy, whichever is earlier, or any AE that is considered treatment related regardless of the start date of the event. Patients are counted only once for any given event, regardless of the number of times they actually experienced the event. The event with the worst toxicity grade is used. If a patient has all adverse events with missing toxicity grades, the patient is only counted in the total column.

Conclusions

PROTEUS sets a new standard of care in HR-LPC

Unprecedented Study Design

- Largest size to date
- Novel end points
- PSMA-PET inclusion

Enhanced Disease Control of RP

Significant benefit:

- 9× greater pCR/MRD
- 20% less risk of MFS
- 29% less risk of recurrence or death
- 3 years longer time to next treatment

Known Safety Profile

Tolerability of APA+ADT consistent with prior studies

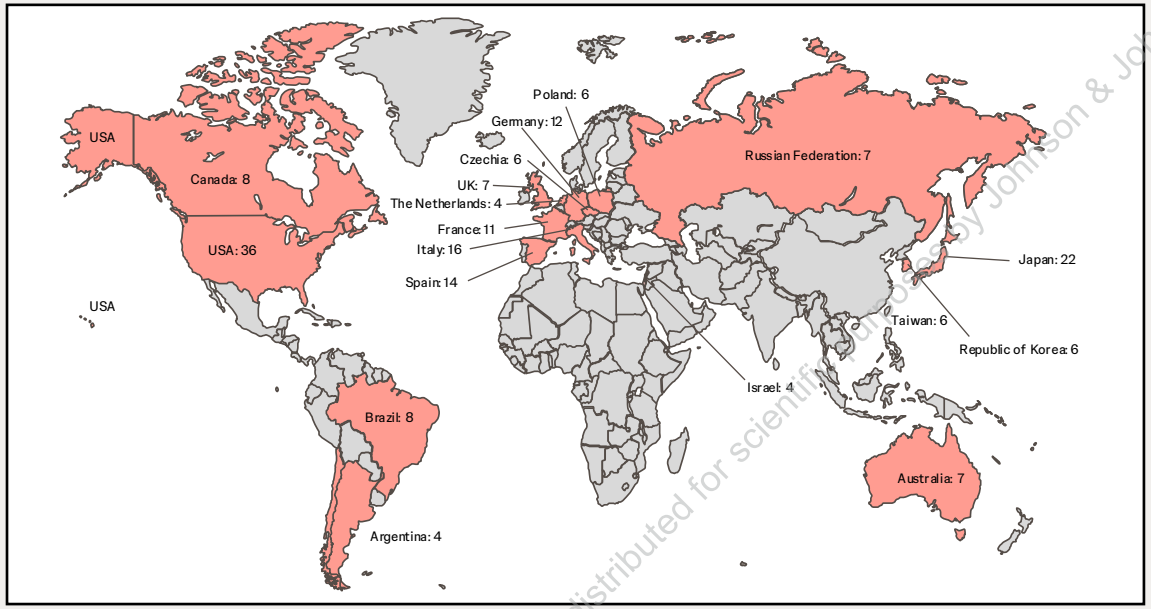
More to Come

- Substudy comparing with direct RP
- Biomarker assessment
- Surgical outcomes
- Pathology correlates

Acknowledgments

Thank you to our patients, their families and caregivers, PROTEUS investigators, site staff, and clinical teams

A total of 2109 patients from 184 sites in
18 countries were randomized in PROTEUS



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Medical writing assistance was provided by Ann Tighe, PhD, and Larissa Belova, PhD, of Parexel, and funded by Johnson & Johnson.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Apalutamide in High-Risk Localized Prostate Cancer

M.-E. Taplin,[1] M. Gleave,[2] N.D. Shore,[3] A. Lopez-Gitlitz,[4] A. Kretschmer,[5] E. Efstathiou,[6] P.L. Nguyen,[7,8] R. Damião,[9] T. Kamoto,[10] A. Ross,[11] A. Briganti,[12] B.A. Hadaschik,[13,14] A. Heidenreich,[15] Á. Juárez Soto,[16] H. Ye,[17] G. Gotto,[18,19] B. Rooney,[20] S.K. Tian,[5] L. Wetherhold,[5] B. Miladinovic,[21] S.A. McCarthy,[5] C.P. Evans,[22,23] and A.S. Kibel,[7,8] for the PROTEUS Investigators*

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